Opiates and Opiate Antagonists

ADVANCES in knowledge of the clinical uses of the recently discovered opiate antagonists nalorphine and levallorphan in the treatment of opiate and opioid poisoning, and the use of these drugs in the diagnosis of narcotic addiction, are reviewed in this monograph. Also discussed is the abuse of narcotic drugs, including the neurophysiological and psychological mechanisms of intoxication, pharmacogenic dependence, and relapse after cure.

Clinical Uses of Opiate Antagonists

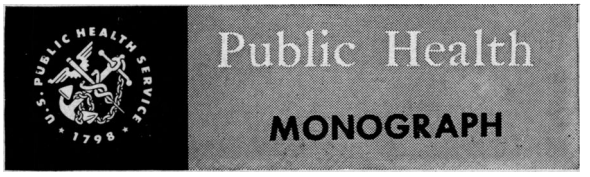
In human subjects, nalorphine produces autonomic effects resembling those of morphine, but often it also produces hallucinatory and other mental disturbances, particularly after repeated doses or large single doses. In man, nalorphine has analgesic properties, and repeated doses do not produce addiction (physical dependence), but its "side effects" impair its clinical usefulness in the management of pain. In medical practice, nalorphine has been used primarily for resuscitation of patients poisoned by overdoses of morphine, heroin, methadone, dihydromorphinone, pantopon, levorphan, meperidine, or alphaprodine. In such cases, the most prominent narcotic antagonistic effects are those exerted on respiratory depression. In subjects addicted to morphine, methadone, heroin, and many other opiates and opioids (except possibly meperidine), nalorphine precipitates acute "abstinence syndromes" and has therefore been used clinically in the diagnosis of active addictions. Analysis of dose-effect relationships both in man and in animals suggests that nalorphine and its analogs exert their "specific" narcotic-antagonistic actions by (*a*) "molecular competition" and (*b*) "unmasking" of the processes responsible for the opiate and opioid abstinence syndromes.

Narcotic Drug Abuse

The problems of narcotic drug abuse include "euphoria," "addiction," and "habituation," and these are considered both from the neurophysiological and psychological viewpoints.

The distinction between "positive" and "negative" euphoria is discussed, and the latter is considered mainly from the standpoint of mechanisms involved in the production of morphine analgesia.

Neurophysiological data obtained chiefly in studies on "analgesic-test" reflexes in animals indicate that morphine exerts selective depressant actions on interneuronal activity in the spinal cord, medulla, midbrain reticular forma-



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The accompanying summary covers the principal findings presented in Public Health Monograph No. 52, published concurrently with this issue of Public Health Reports. The author is with the National Institute of Mental Health Addiction Research Center, National Institutes of Health, Public Health Service, Lexington, Ky.

Readers wishing the report in full may purchase copies of the monograph from the Superintendent of Documents, Government Printing Office, Washington 25, D. C. A limited number of free copies are available to official agencies and others directly concerned on specific request to the Public Health Service. Copies will be found also in the libraries of professional schools and of the major universities and in selected public libraries.

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Wikler, Abraham: Opiates and opiate antagonists. A review of their mechanisms of action in relation to clinical problems. Public Health Monograph No. 52 (PHS Pub. No. 589). 39 pages. U. S. Government Printing Office, Washington, D. C., 1958. Price 30 cents.

tion, lateral posteroventral, and certain of the medial thalamic nuclei and cerebral cortex, while also exerting excitant actions at all levels and augmenting supraspinal inhibition.

Evidence acquired in studies on both man and animals indicates that one of the important psychological actions of morphine is reduction of pain-anticipatory anxiety. Other actions of morphine that may be involved in the production of euphoria are discussed with particular reference to personality factors.

The neurophysiological effects on the morphine abstinence syndrome of bilateral frontal lobotomy and physiological "transection" of the spinal cord in man (due to disease), and of decortication and spinal transection in the dog, indicate that the processes responsible for addiction operate at cellular (neuronal) levels throughout the neuraxis and appear to involve "counter-adaptations" to the depressant effects of morphine on interneuronal activity. While data obtained in frontal lobotomized patients and in monkeys subjected to bilateral frontal lobectomy, bilateral cingulumotomy, or bilateral ablation of the cingulate gyri are conflicting in some respects, it appears that although the integrity of the cerebral cortex and its connections with subcortical structures is necessary for the expression of "purposive" abstinence phenomena, the "nonpurposive" features of the morphine abstinence syndrome are integrated to a very large extent subcortically. In addition, studies on man indicate that during morphine addiction, adrenal and gonadal activities are depressed, probably through an indirect effect on the pituitary gland, and that transient "rebound" adrenal hyperactivity occurs on withdrawal of the drug.

In considering the psychological aspects of addiction, it is stressed that with the development of tolerance the "euphoric" effects of morphine become progressively attenuated, but that new sources of gratification are developed as a consequence of the progressively intensified "need" for the drug. The "rewarding" effects of morphine include the periodic relief of "craving," the sense of achievement engendered by successful pursuit of drug supplies ("hustling"), and social acceptance of the user by other addicts. Also, the suffering attendant upon abrupt and complete withdrawal of the drug may serve some addicts as a means of expiating guilt.

The role of "conditioning" in the genesis of relapse (habituation) is discussed from both "classical" and "instrumental" theoretical viewpoints. A number of suggestive, but not conclusive, observations indicate that the opiate abstinence syndrome may become "conditioned" to regularly associated environmental stimuli. If verified, such a process could account, in part, for the motivation to relapse under certain circumstances long after the "unconditioned" morphine abstinence syndrome has subsided. Data more strongly supported by experimental evidence, obtained in rats, indicate that the recurrent reduction of abstinence distress during maintained morphine addiction can result in reinforcement of such of the organism's activities as culminated regularly in administration of the drug, and that in consequence, "drug-seeking" behavior may persist beyond the duration of the "unconditioned" abstinence syndrome.

It appears likely, therefore, that the probability of relapse is not only a function of the initial "euphoric" effects of opiates, which diminish rapidly as tolerance develops, but also of the cyclic actions of these agents in generating dependence and in relieving abstinence symptoms. These actions persist as long as the opiates are administered at sufficiently high dose levels and at sufficiently frequent intervals. The probability of relapse is also related to the extent to which the administration of these drugs is brought about by actions of the organism upon its environment. In addition, theoretical considerations suggest that "secondary reinforcers," or stimuli regularly associated with reduction of abstinence distress during maintained addiction, may serve as incentives for subsequent relapse.

Although practically nothing is known about the neurophysiological mechanisms operating in relapse, progress in that direction, as well as in the further elucidation of the psychological processes involved, may become possible with continued improvement of recently developed techniques for demonstrating in animals a "model" of this most important of all problems of drug abuse.